Citation:

Shai I, Schwarzfuchs D, Henkin Y, Shahar DR, Witkow S, Greenberg I, Golan R, Fraser D, Bolotin A, Vardi H, Tangi-Rozental O, Zuk-Ramot R, Sarusi B, Brickner D, Schwartz Z, Sheiner E, Marko R, Katorza E, Thiery J, Fiedler GM, Blüher M, Stumvoll M, Stampfer MJ; Dietary Intervention Randomized Controlled Trial (DIRECT) Group. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. *N Engl J Med.* 2008 Jul 17;359(3):229-41.

PubMed ID: 18635428

Study Design:

Radomized Controlled Trial

Class:

A - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To compare the effectiveness and safety of three diets: a low-fat, restricted calorie diet; a Mediterranean, restricted calorie diet; and a low-CHO, non-restricted calorie diet.

Inclusion Criteria:

- 40 - 65 years of age
- BMI ≥ 27 or the presence of type 2 diabetes or coronary heart disease regardless of age and BMI

Exclusion Criteria:

- Pregnancy or lactation
- Serum creatinine level ≥ 2 mg/dl
- Liver dysfunction
- Gastrointestinal problems preventing adherence to any of the test diets
- Active cancer
- Participation in another diet trial

Description of Study Protocol:

Recruitment Began December 2004 in a workplace at a research center.

Design Randomized controlled trial with random assignment to one of three diet interventions within strata of sex, age, BMI, history of coronary heart disease, history of type 2 diabetes, current use of statins by Monte Carlo simulations. Each of the three diet groups had six subgroups of 17 -

19 participants assigned to an RD. Each subgroup met with their assigned RD in weeks 1, 3, 5, and 7 followed by 6 week intervals over 2 years for 90 minute workshops. Six times during the study another RD conducted 10 - 15 minute motivational phone calls with subjects.

Blinding used (if applicable) Clinic and lab staff were blinded as were study coordinators.

Intervention (if applicable)

- *Low Fat restricted-calorie diet* was based on AHA guidelines. Target was 1500 kcal for women and 1800 kcal for men with 30% from fat, 10% from saturated fat, and 300 mg cholesterol per day.
- *The Mediterranean diet* was moderate-fat, restricted-calorie with 1500 kcal for women and 1800 kcal for men with up to 35% fat. Main sources of added fat were 30 - 45 g of olive oil and a handful of nuts (<20 g) per day.
- The *Low CHO non-restricted-calorie diet* aimed for 20 g CHO per day for the first 2 months with a gradual increase to a maximum of 120 g per day. Intakes of total calories, protein and fat were not limited based on the Atkins diet.

Statistical Analysis

- ANOVA was used to analyze dietary intake values between groups at each time point
- Pairwise comparisons among the diet groups were determined by Tukey's Studentized range test
- Intention-to-treat analyses included all subjects with most recent values for weight and BP
- Cross-sectional time-series analysis was used for panel data analysis
- Non-independence of repeated measure was controlled for
- Age, sex, time point, and diet group were independent variables
- Interaction terms were used to control for effects of sex or diabetes
- Within-person changes from baseline in each diet group were analyzed by pairwise comparisons
- A power test was conducted to determine weight loss differences with a type 1 error of 5%, 100 subjects per group, and significance of 90%.

Data Collection Summary:

Timing of Measurements Baseline and monthly for weight and waist circumference; every 3 months for BP, blood samples at baseline, 6, 12, and 24 months

Dependent Variables

- Weight without shoes
- Waist circumference measured halfway between last rib and iliac crest
- BP by automated system 5 minutes after rest
- Serum lipids
- FBG
- Inflammatory biomarkers and leptin (C- reactive protein, adiponectin)
- Plasma insulin
- Liver enzymes and bilirubin (alk phos, ALT)

Independent Variables

- Three diets

- *Low Fat restricted-calorie diet* was based on AHA guidelines. Target was 1500 kcal for women and 1800 kcal for men with 30% from fat, 10% from saturated fat, and 300 mg cholesterol per day.
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Control Variables

- Age
- Sex
- Smoker

Description of Actual Data Sample:

Initial N:

- 625 screened (303 were excluded, 259 declined to participate, 20 did not participate due to other reasons)
- 322 randomized to diet intervention (86% males), 272 completed the study (reasons for dropouts were lacked motivation, sabbatical, personal reasons, or disappointment with assigned diet)
- 322 used for primary analysis

Attrition (final N): 272

Age: 52 ± 7 years of age (LF diet = 51 ± 7 yrs; Med diet = 53 ± 6 yrs; LC diet = 52 ± 7 yrs)

Ethnicity: not mentioned

Other relevant demographics:

Anthropometrics At baseline:

Measure	LF Diet	Mediterranean Diet	LC Diet	All
Weight (kg)	91.3 ± 12.3	91.1 ± 13.6	91.8 ± 14.3	91.4 ± 13.4
BMI	30.6 ± 3.2	31.2 ± 4.1	30.8 ± 3.5	30.9 ± 3.6

Means ± SD

Location: Israel

Summary of Results:

Key Findings

- Overall rate of adherence was 95.4% at 12 mos. and 84.6% at 24 mos (at 24 mos 90.4% for LF, 85.3% for Med, 78.0% for LC, p = 0.04 for comparison among diet groups).

- Daily energy intake decreased for all groups at 6, 12, and 24 mos ($p<0.001$) without differences among groups in amount of decrease.
- The LC group had the most subjects (8.3%, $p = 0.04$) with urinary ketones at 24 mos.
- Maximum wt loss occurred from 1 - 6 mos. with maintenance from 7 - 24 mos. All groups lost weight with greatest loss for the LC and Med groups ($p<0.001$) for interaction of group and time.
- All groups had significant decreases in waist circumference and BP without differences among groups.
- All groups increased HDL-C with the greatest increases in the LC group (8.4 mg/dl, $p< 0.01$) compared with the LF group.
- TG decreased significantly in the LC group compared with the LF group, $p=0.03$.
- LDL levels did not change significantly within groups or among groups.
- TC:HDL improved overall with the greatest relative decrease (20%) in the LC group compared with the LF group, $p=0.01$.
- CRP decreased significantly ($p<0.05$) only for the Med and the LC groups with no difference between groups.
- Adiponectin increased in all diet groups ($p=0.05$) without difference between groups.
- Leptin decreased in all groups ($p<0.05$) without difference between groups. There was a greater decrease in leptin for men ($p=0.04$) for an effect of sex and diet in the LC group compared to the LF group.
- Among 36 subjects with diabetes only those in Med group had a decrease in FBG while FBG rose in subject with diabetes in the LF group, $p<0.001$. No significant difference in FBG for those without diabetes.
- Insulin levels decreased in all participants without differences among groups.
- Among those with diabetes the homeostasis model assessment of insulin resistance (HOMA-IR) at 24 mos. was greater for the Med group than for the LF group, $p=0.02$,$p=0.04$ respectively. (This was determined to not be a sensitive marker of insulin sensitivity.)
- Among those with diabetes, glycated Hgb at 24 mos decreased the most for the LC group, $p=0.45$.
- Changes in bilirubin, alkaline phosphatase, and ALT were similar among diet groups.

Dietary Intake Changes (means $\pm$ SD)

Variable	LF Diet	Med Diet	LC Diet	P Value For differences among groups
Energy from baseline (kcal/d)				
6 mo	-458.3 $\pm$ 1412.9	-254.6 $\pm$ 740.6	-560.8 $\pm$ 1568.3	0.22
12 mo	-559.1 $\pm$ 1764.8	-321.7 $\pm$ 802.4	-591.1 $\pm$1472.9	0.33
24 mo	-572.6 $\pm$ 1638.0	-371.9 $\pm$ 864.2	-550.0 $\pm$ 1453.9	0.55
CHO % of kcals				
6 mo	50.4 $\pm$ 6.9	49.8 $\pm$ 8.0	41.4 $\pm$ 9.3*	<0.001
12 mo	50.5 $\pm$ 6.8	50.0 $\pm$ 7.7	41.6 $\pm$ 8.8*	<0.001
24 mo	50.7 $\pm$ 5.7	50.2 $\pm$ 8.6	40.4 $\pm$ 7.1*	<0.001
Pro % of kcals				
6 mo	19.6 $\pm$ 3.7	18.9 $\pm$ 3.6	21.6 $\pm$ 3.5*	<0.001
12 mo	19.4 $\pm$ 3.4	18.9 $\pm$ 3.6	21.5 $\pm$ 4.0*	<0.001
24 mo	19.0 $\pm$ 3.2	18.8 $\pm$ 3.5	21.8 $\pm$ 3.9*	<0.001

Fat % of kcals				
6 mo	30.7 ± 4.0	33.2 ± 5.1	38.8 ± 6.9*	<0.001
12 mo	30.8 ± 4.2	32.9 ± 5.1	38.5 ± 6.5*	<0.001
24 mo	30.0 ± 3.9	33.1 ± 5.5	39.1 ± 5.5**	<0.001

*LC different from Med or LF groups, p<0.05; **LC different from the LF group, p<0.05

Changes in Dependent Variables from Baseline to 24 Months (mean ± SD)

Measure	LF Diet	Med Diet	LC Diet	P Value for difference among groups
Weight Change, kg (n=322)	-2.9 ± 4.2	-4.4 ± 6.5	-4.7 ± 6.5	P not given
Weight Change, kg (n=272 completers)	-3.3 ± 4.1	-4.6 ± 6.0	-5.5 ± 7.0	P=0.03 for LF v LC
BMI	-1.0 ± 1.4	-1.5 ± 2.2	-1.5 ± 2.1	P=0.05
Waist circumference, cm	-2.8 ± 4.3	-3.5 ± 5.1	-3.8 ± 5.2	P=0.33
BP mmHg systolic/diastolic	-4.3 ± 11.8/ -0.9 ± 8.1	-5.5 ± 14.3/ -2.2 ± 9.5	-3.9 ± 12.8/ 0.8 ± 8.7	P=0.64/ P=0.43
Serum HDL-C, mg/dl Means only	6.4	6.3	8.4	P=0.94 for LF v Med; p=0.01 for LF v LC
Serum TG, mg/dl Means only	-2.8	-21.8	-23.7	P=0.21 for LF v Med; P=0.03 for LF v LC
Serum LDL-C, mg/dl Means only	-0.05	-5.6	-3.0	P=0.41 for LF v Med; P= 0.94 for LF v LC
TC:HDL, means only	-0.6	-0.9	-1.1	P=0.23 for LF v Med; P=0.01 for LF v LC
C-reactive protein, mg/L, means only	-0.5	-0.9	-1.3	P=0.49 for LF v Med; P=0.12 for LF v LC
FBG, mg/dl, means only	12.1	-32.8	1.2	P=<0.001 for LF v Med; P=0.12 for LF v LC
Insulin, uU/ml, Means only	-1.5	-4.0	-2.2	P=0.78 for LF v Med; P=0.2 for LF v LC

Hgb A1C, %	-0.4 ± 1.3	-0.5 ± 1.1	-0.9 ± 0.8	p= 0.45 among groups; p<0.05 for LC from baseline

N = 263 for lipid values and C-reactive protein; n=36 (those with diabetes) for FBG, insulin, and Hgb A1C

Other Findings

- No significant difference among groups with change in medication usage.
- No significant differences among groups with respect to composition of diets at baseline.
- The amount of physical activity increased in all groups without differences among groups.

Author Conclusion:

More than one dietary approach may be considered for weight loss according to preferences and metabolic needs. The Mediterranean and low-CHO diets are effective alternative to the low-fat diet for weight loss. More favorable effects on lipids were found with the low CHO diet and on glycemic measures with the Mediterranean diet.

Reviewer Comments:

- *Standard deviations are available for all outcome measures but difficult to identify exact values from figures for some.*
- *Strengths include long (2 year) duration of study, relatively high compliance rate, a one-phase design, and relatively large N, the % of kcals from fat in the LF = 25.9 ± 8.0, Med = 31.7 ± 9.1, LC = 40.5 ± 10.0 which were significantly different among groups.*
- *Limitations include few woman enrolled (86% male), few subjects with diabetes, dietary intake was self-reported and this was used to determine compliance, unique nature of workplace which may not represent free-living populations, absolute values of energy intake not provided and LC diet may have been hypocaloric even though the energy was not meant to be restricted, and LC subjects were counseled to select vegetarian sources of fat and protein which is not congruent with the Atkins diet.*

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions

1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	Yes
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes

3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	Yes

Validity Questions

1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	???
3.	**Were study groups comparable?**	Yes
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	Yes
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	Yes
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	Yes
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	N/A
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A

3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	Yes
4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	Yes
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	No
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	N/A
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	Yes
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	N/A
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	Yes
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A

6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	Yes
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes
7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	Yes
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
8.6.	Was clinical significance as well as statistical significance reported?	Yes
8.7.	If negative findings, was a power calculation reported to address type 2 error?	N/A
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**	Yes
9.1.	Is there a discussion of findings?	Yes
9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**	Yes

10.1.	Were sources of funding and investigators' affiliations described?	Yes
10.2.	Was the study free from apparent conflict of interest?	Yes